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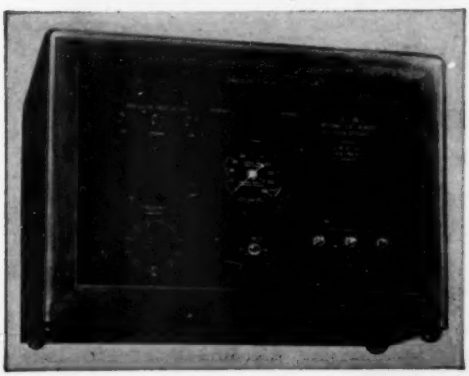

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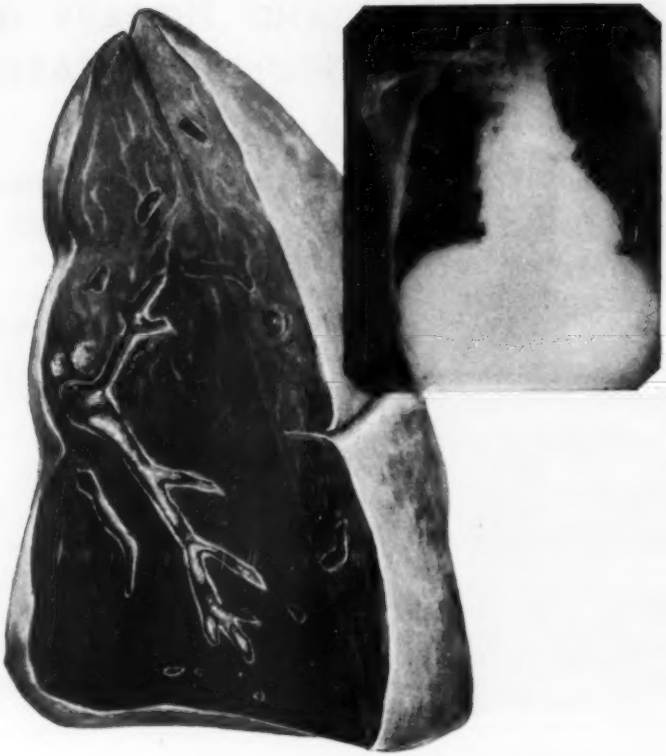

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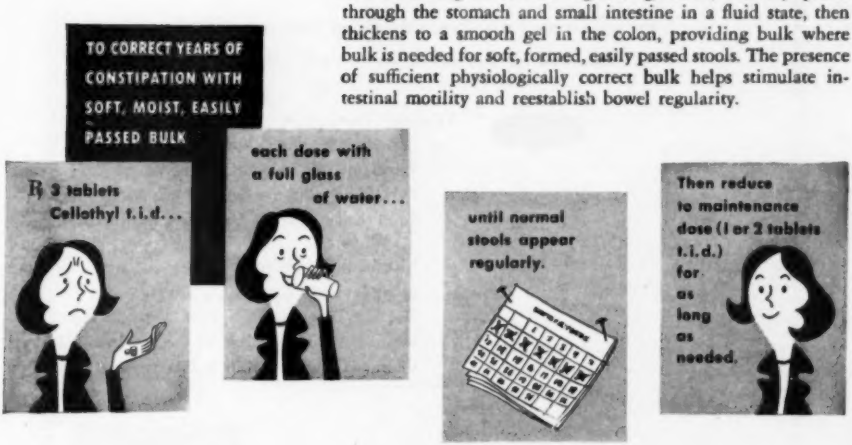
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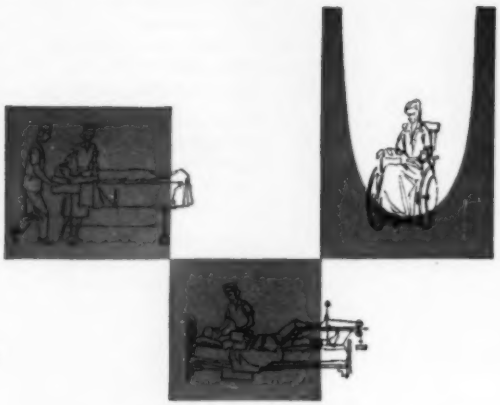

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 27, NO. 11 NOVEMBER 1951

ADDRESS OF WELCOME TWENTY-FOURTH GRADUATE FORTNIGHT*

WILLIAM BARCLAY PARSONS

President, The New York Academy of Medicine

It is a privilege and pleasure to welcome all of you on behalf of The New York Academy of Medicine to the first session of its twenty-fourth Graduate Fortnight, which now is officially opened.

Twice before, in 1931 and in 1941, certain aspects of disease of the circulatory system formed the basic subject matter for discussion. The Committee in charge of arranging the program for this Fortnight decided that there have been sufficient advances during the past ten years to make it almost mandatory to take the Disorders of the Circulatory System as the subject matter for discussion.

The Academy welcomes the collaboration of the New York Heart Association in this Graduate Fortnight. As you can see from the program its President, Dr. Irving S. Wright, and Vice President, Dr. Charles A. Poindexter, have been active members of the main Committee and have contributed greatly in the preparation of the program. All the members of the Committee have done a magnificent job and we owe them a heartfelt vote of thanks. In particular we should mention

* Given 8 October, 1951 at the 24th Graduate Fortnight of The New York Academy of Medicine.

Dr. William Dock, who as Chairman of the whole Committee, worked out the program and saw to it that the various sub-committees completed their assignments; Dr. Alfred Angrist who has planned and executed the Exhibit; and Dr. Clarence de la Chapelle who has arranged the Panel Discussions. To Dr. Mahlon Ashford, who has resigned after many years of service as Executive Secretary of the Committee on Medical Education, we owe an especial debt of gratitude. His has been the guiding hand that over the years has made these Graduate Fortnights such outstanding successes. Although behind the scenes, quiet and unobtrusive, his organizing genius has simplified the duties of the volunteer committees and I feel sure that each one of them agrees with me. Our thanks are due to our friends here in town who will deliver papers, hold demonstrations or have prepared exhibits. Lastly I thank on behalf of the Academy our visitors from out of town: Drs. Blumgart, Gofman, Szent-Györgyi, Dexter, Stead, Katz, Page, Duryee, Sosman and Hunter, who have come from North, West and South to make their contributions for our interest and education in those subjects in which they are admittedly masters.

The program for the evening meetings covers metabolism, chemistry, physiology, surgery, radiology, psychiatry and therapeutics. The clinical meetings in various hospitals will cover a wide field of subjects, and the exhibits here in the Academy do not fall short of the excellence of previous years. We are sure that the menu which is in your hands indicates that a highly nutritious mental repast has been prepared for your enjoyment. I therefore wish you "Bon appetit."

THE MECHANISM AND MANAGEMENT OF CIRCULATORY FAILURE*

WILLIAM DOCK

Professor of Medicine, State University of New York, State University Medical Center at New York, College of Medicine, Brooklyn, New York

CIRCULATORY failure exists when any tissue, or the body as a whole, receives less than an optimal blood flow. Often the failure is local, as when the retina receives inadequate blood in a pilot pulling his airplane out of a dive, or when the myocardium is poorly perfused because of coronary sclerosis. General failure occurs when the minute volume flow of blood into the aorta fails to meet the needs of the whole body. This happens in all of us on exertion, and leads to oxygen debts of varying magnitude. Such deficits in flow are made up after exertion ceases. Acute failure also occurs after severe hemorrhage, or with venous pooling due to reclining at a 75° angle on a tilt table, or after taking nitrites while quiet and erect. In all these conditions the roentgen shadow of the heart decreases, the rate becomes rapid, and blood pressure is normal or low. As the systolic pressure falls toward or below 90 mm Hg., and the patient develops nausea and apathy, circulatory failure progresses into shock. This can occur from dehydration, adrenal insufficiency, or hepatic necrosis as well as from trauma and hemorrhage.

Peripheral circulatory failure may be due entirely to decrease in blood volume, or, as in spinal cord lesions, entirely to loss of vasomotor and venomotor tone. In many acute infections and intoxications, both factors are present. Restoration of blood volume by transfusion will not completely relieve the disorder if venomotor and vasomotor tone are lost, nor will restoration of vascular tone, by norepinephrine infusion, give complete relief if blood volume is greatly reduced. Combinations of both forms of therapy now permit far better control of peripheral circulatory failure than ever before. Shorr's investigations of the epinephrine antagonists have not yet led to specific therapy for the loss of tone in arterioles and precapillary sphincters due to high levels of vaso-

* Presented before the 24th Graduate Fortnight, of The New York Academy of Medicine, October 10, 1951.

depressor material of hepatic origin, although this type of shock has been corrected by dialysis of the blood in the artificial kidney.

Circulatory failure of the acute peripheral type is compensated for by the body, as we may see after hemorrhage, by rise in venomotor and arteriolar tone, and by conservation of sodium chloride and water. The latter, effected by endocrine control of the kidney, permits restoration of blood volume and tissue turgor. Also there is a new formation of plasma protein and of red cells, so that the blood lost is soon fully replaced. Cardiac output falls when we are in the sitting or erect posture, and in studies of patients with postural hypotension, whose beds are tilted so the shoulders are well above the legs throughout both day and night, a rise of several hundred ccm. in blood volume occurs in a week or two.[1] The body brings into play all these restorative reflexes, whether circulatory failure is due to hemorrhage, posture, or to any other cause.

In peripheral failure cardiac output falls because venous return and ventricular filling are inadequate. When the pericardial sac is distended with fluid, or the pericardium scarred and drawn tight around the ventricles, heart failure is due largely to inadequate diastolic filling of the ventricles. These conditions usually develop slowly, and as the compensatory reflexes come into play, there is a rise in blood volume and in body water far above the normal level. Combined with the rise in tone of venules, this raises pressure in the auricles, but does little to improve ventricular filling when there is high resistance due to pericardial disease.

These forms of circulatory failure might be considered as preventricular, in analogy with prerenal uremia or edema, while the common form of circulatory failure, congestive heart failure, is in most instances ventricular or myocardial. The fundamental problem of myocardial failure is one with which only those who have Prof. Szent-Györgyi's experience and imagination can deal. It is the problem of muscular fatigue in the special biochemical setting of the heart muscle, fatigue in a muscle which must contract at least thirty times a minute to maintain our vital functions. Why do hearts carry their heavy burdens for decades, and fail even when less is demanded of them in senescence, and why is this sort of failure reversed, to some degree, by digitalis glucosides? These are the problems now being attacked by the biochemist. It is simple enough for the clinician to explain to himself the failure of

a muscle inflamed by myocarditis, or of myocardial cells filled with glycogen or buried in amyloid. Since none of these simple causes are present in most cases of heart failure at ages over 40, the clinician seeks an explanation from the biochemists, whose progress is most exciting, even though we catch only fleeting glimpses through our fog of ignorance.

In chronic cardiac failure—failure of the ventricles to expel in systole the blood which overfills them in diastole—all of the compensatory mechanisms seen after hemorrhage are at work, and the patient has a high blood volume, excessive extracellular fluid, and yet continues to retain sodium and water.[2] If depleted of sodium, his renal function may fail and his plasma sodium fall to critical levels, because he still retains water in excess of his osmotic needs. These results of the body's compensation for inadequate output of blood cause most of the symptoms of heart failure, and will be considered in detail by other speakers. But it must be emphasized that the rate at which symptoms increase, and the severity of the symptoms observed do not give a valid index of ventricular fatigue, but are usually functions of the excess of the patient's salt intake over the normal needs of the mammalian body. The latter, for sedentary people in temperate climates, does not exceed 200 mgm of sodium per day, while American diets provide three to eight thousand mgm a day. This excess makes rapid accumulation of edema easy, even with mild degrees of ventricular failure which would not be apparent with physiologic levels of sodium ingestion.

The physician is chiefly concerned with congestive failure occurring in middle age, in sedentary people, with the usual excessive salt intake. Symptoms develop rapidly in such patients whenever cardiac output falls a little below optimal needs of the body and when salt ingestion suddenly rises. The optimal needs for flow include not only the blood to keep oxygen tension at proper levels in all organs and replace oxygen debts due to exertion, but blood to maintain normal flow to the renal filter, to the dermal heat-radiating system, and to any leaks or shunts in the circulation. When thiamine deficit sets in, additional cardiac output is needed. Pyruvate seems to act as a vasodilator and keeps the vascular bed open even when all other needs have been met. In cirrhosis of the liver, open shunts in the skin and elsewhere may double blood flow in relation to normal basal needs. Failure to meet all such excessive demands may lead to severe symptoms of heart failure at

cardiac outputs far above normal. This is similar to uremia in a patient with two or three times the normal daily output of nitrogenous metabolites, due to high protein intake or rapid break-down of body protein.

It might be thought that such increases in demand for blood flow would be important direct causes of heart failure. Actually the cost to the heart muscle of increasing stroke volume when the peripheral resistance falls is remarkably small. During exercise in normal people stroke volume rises but heart volume falls. Since oxygen use by the heart varies with heart volume,[3] the fall in resistance must more than compensate for the rise in stroke volume, which can thus be maintained at reduced levels of oxygen use per beat. We may conclude that the burden on the heart, due to increased volume flow of blood, is usually less than one would think from the rise in pulse rate. Such acceleration regularly occurs with increase in venous return.

Arterial hypertension, whether systemic or pulmonic, also adds to the burden of the ventricle, but we have no way to measure how much. Systemic pressure may gradually double, and pulmonic pressure rise four or five-fold yet heart failure may not set in, and ventricular volume increases far less than one would calculate from Starling's curves relating cardiac work to cardiac volume.[4] The curves deal with acute situations, and with an acute rise of pressure, heart failure may occur as would be predicted. In chronic disease, the muscle cells become thick, not long, and the work is done very efficiently. In such patients, rise in rate, not the level of pressure, is the best clue to the cardiac burden per gram of muscle. Even in acute experiments, doubling the systemic pressure level increases work per gram of muscle only 25 to 30 per cent.

Doubling the rate imposes on the heart, beating at constant volume, an increase in oxygen need of only 50 per cent per minute, and reduces oxygen used per beat.[4] But rise in rate also shortens the time available for restoration of the molecular arrangements and high energy chemical bonds needed for contraction. The evidence from clinical experience points to slowing down of these chemical reactions in myocarditis and in the aging heart, thus making the ventricles especially prone to fatigue or partial exhaustion of contractile force if driven at rapid rates. While elderly patients with complete heart block may have low minute volume flow, and are unable to increase this much on exertion, they do maintain high stroke volumes against normal or high arterial resistance, and rarely show classical evidence of congestive failure. Even when they

have had previous myocardial infarction and have bundle branch block, they usually have large ballistocardiographic waves of normal contour. This indicates vigorous ejection of a large stroke volume by the slowly beating heart.

At the opposite extreme we see that when young people with normal hearts have an attack of paroxysmal tachycardia, heart failure develops in a day or two. In the first hours, the heart is small, as seen by x-ray, just as with the tachycardia of exercise, but it gradually dilates as it becomes fatigued by sustained rates over 180 per minute, and in one or two days, venous pressure rises, rales develop in the lungs and the liver becomes swollen and tender. With termination of the rapid rate, everything returns to normal in a few days. There can be no doubt in the minds of those who study cases of block on one hand and of tachycardia on the other that that acceleration of the heart is the most potent factor in causing heart failure. Because increase in minute volume flow is regularly associated with acceleration in rate, it too has a causative role far greater than would be the case if stroke volume alone were increased. Cardiac acceleration is a common sequel of anger, apprehension and related moods, so that heart failure may be precipitated by emotional storms, just as it is by fever and by other conditions, such as beriberi, hyperthyroidism or cirrhosis which accelerate the pulse. As the average age groups of patients increases, heart failure occurs more often as a result of a given degree of acceleration, or of change in stroke and resistance. Also, acceleration causes failure to develop more quickly in older people and the rise in rate required to cause failure becomes less marked. At age twenty-five, heart failure does not occur in normal hearts driven less than 150 per minute; at ages over fifty it often occurs at rates of only 100 to 120, and disappears when the rate falls below 80.

It was long taught that failure of the coronary bed to grow, and inability of oxygen to diffuse into thick fibers, could explain myocardial failure in hypertrophied but otherwise presumably normal ventricles. Bing and Goodale[5] have shown that flow is normal and oxygen uptake is high in hypertrophied hearts without coronary sclerosis, and it is now realized that oxidation can occur by electron transfer along long molecules so that the calculations on diffusion into fibers have become less significant.[6] Today we can assume that chronic heart failure due to anoxia occurs only with coronary occlusion or with anemia of extreme severity. Acute anoxia due to ischemia or anemia can develop

swiftly in shock and hemorrhage, and may precipitate failure of the myocardium and acute pulmonary edema. But, in striking contrast to these types of failure is the extreme infrequency of chronic myocardial failure with congestive phenomena in younger subjects with fatal coronary sclerosis. This was evident in the hundreds of soldiers under thirty-five years of age, whose deaths were studied at the Army Institute of Pathology[7] and also in young civilians.[8] Even with myocardial necrosis and ischemia, heart failure is most uncommon before the age of forty. In the light of our present knowledge, myocardial necrosis and scarring, and coronary insufficiency, contribute to the work of the ventricles, cause pain, cardiac irregularities and tachycardia due to apprehension, but coronary insufficiency or failure of the coronary bed to hypertrophy are not the direct causes of the fatigability of the ventricular muscle which underlies myocardial failure. Pain, not fatigue, is the result of ischemia in voluntary and in cardiac muscles.

The failure of a heart which has lost myocardial efficiency or the ability to restore its molecular machinery rapidly after each beat is therefore hastened more by acceleration than by other factors, while the rate of evolution of symptoms depends largely on the daily intake of sodium. Symptoms also are aggravated by other stimuli to salt retention, the most common being operative shock and premenstrual steroid stimulation of renal reabsorption of sodium. The most readily demonstrable and easily corrected cause of myocardial fatigability are abnormal levels of plasma potassium and a deficiency of water-soluble vitamins, specifically thiamine. All the other causes are vague and hypothetical, but some of them may be corrected, in part, by digitalis. The cardiac glucosides may also reverse the ill effects on the heart of high or low potassium levels, and of excessive dosage of desoxycorticosterone.

From this schematic description of heart failure, the general principles of therapy are obvious. Therapy is most successfully directed at the phenomena due to attempted restoration of optimal output—that is, the increase in blood volume and the retention of sodium. Bleeding, when hemoglobin levels are over 12 gm per cent, the liver large and the neck veins full, not only relieves the engorged venous system but may actually lead to a rise in cardiac output, by relieving over-dilation and tachycardia. Sodium depletion, by diet, mercury and cationic exchange resins, not only relieves pulmonary edema but by reducing myocardial edema may improve the function of the ventricles. Thus,

therapy directed at secondary phenomena which cause distress may actually improve cardiac function.

Slowing the heart is of utmost importance, and this may occur merely through relief of fright, when the patient has confidence that the doctor is competent and diligent. This deceleration is further helped by judicious use of a narcotic for a day or so, and sedation thereafter. It may be greatly assisted by a cool oxygen tent, if the patient is not alarmed or annoyed by this device. A decrease in symptoms is often effected by proper posture alone. Often in urgent dyspnea the most restful posture is sitting in the arm chair before a table piled with pillows on which the patient can lean forward. In some cases an ordinary bed, with the head end tilted up so the whole bed is at 30°, is more comfortable than the propped-up Gatch bed. On a tilted bed the patient can roll on his side, or lie prone.

Digitalis is of greatest value when it slows the ventricles in auricular fibrillation, but it may have striking effects on failure with regular rhythm. When given with mercury, diet, sedation, etc. its value can not be assayed; when given after some days on a constant regime it causes no striking benefit in more than half these cases, but in about one-third of the older patients, and occasionally even in children, it clearly is responsible for great improvement in myocardial vigor and relief of symptoms. It should always be given until it gives a good result, or causes coupled rhythm, nausea, or other toxic signs. These latter may be caused by half the average digitalizing dose (1.5 mgm digitoxin, 1.5 gm folia, 0.6 mgm ouabain), or may not occur until twice this dose has been given within 36 hours for digitalis or 6 hours for strophanthin. Perhaps the highest praise a doctor can hope to deserve is the remark my father made of a colleague he greatly admired: "He knows how to use digitalis."

Correction of anemia is an urgent matter in some patients with heart failure and can safely be done with packed red cells. Starvation, disguised as Karrell diet, is usually wrong, although weight reduction is frequently necessary as a long term project. The cardiac needs a simple solid diet, with small frequent feedings and minimal salt intake as long as blood urea is below 80 mgm per cent. Five mgm a day of thiamine is adequate for correction of beriberi heart disease, and is a simple supplement needed by many cardiacs, so that we use it routinely. If there is good reason to suspect Graves' disease, suitable tests and antithyroid

therapy should be undertaken at once. Creatinuria and basal metabolism do not fall in the first few days of therapy, but radioactive isotope studies and protein-bound iodine determination should not be deferred until after therapy is started. All tests are more satisfactory if completed before antithyroid drugs are given. It may, however, be unwise to defer therapy in some cases where the diagnosis is strongly suspected and heart failure is not easily brought under control.

The management of heart failure, which so often begins as an emergency, usually develops into a permanent way of life. In the future, surgery will be more often undertaken to lessen the load on the heart and hypothyroidism eventually induced in cases not otherwise held in check. The fundamental elements for effective control of heart failure are a hopeful, well-instructed patient and a physican who appreciates the hazards of over-cautious regimes, the value of maintaining good morale and bodily fitness, and the need for exhausting simple and reversible forms of therapy before considering those which are costly, hazardous, and irreversible.

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SURGICAL TREATMENT OF PARKINSONISM: INDICATIONS AND RESULTS*

JUDAH EBIN

Clinical Instructor in Neurosurgery, New York Medical College

PARKINSONISM, also known as the parkinsonian syndrome and paralysis agitans, is a disease process which has long held the interest of physicians and research workers. There are several reasons which account for this interest. In the first place, the clinical picture is bizarre, presenting involuntary movements associated with rigidity which ultimately restricts all voluntary movement. Secondly, the plight of victims of this disease is truly pathetic. People of normal appearance are gradually transformed into caricatures of their former selves. The abnormal movements make them conspicuous so that they avoid outside contacts. Their helplessness becomes progressively greater and ultimately they are dependent upon others for assistance in every detail of daily living. Finally, although the disease process has long been studied in an effort to understand its basic mechanisms and provide relief for its victims, full understanding has not been reached. The etiology and pathology of Parkinsonism are for the most part known. However, the pathophysiology of symptoms of the disease is not fully known, and the problems of therapy have been baffling.

The disease is most frequently the manifestation of brain lesions resulting from encephalitis or arteriosclerotic disease. Less commonly it results from syphilitic vascular disease, multiple sclerosis, trauma, alcohol or manganese poisoning. Rarely, a slow-growing, deep intracerebral neoplasm may produce a clinical picture similar to that of paralysis agitans. The lesions are most commonly found in the globus pallidus and the substantia nigra of the midbrain; the thalamus, hypothalamus, putamen and cerebral cortex may also be affected. The chronic encephalitic group is said to show selective bilateral involvement of the globus pallidus and the substantia nigra. The arteriosclerotic group shows widespread pathologic changes, the cerebral cortex being involved as well as the globus

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pallidus and the substantia nigra. Microscopic study has consistently revealed atrophic changes in the ganglion cells of the globus pallidus and the substantia nigra. Deposition of lipochrome pigment in the cytoplasm, and swelling and disintegration of the cells have been noted.

Tremor is the most prominent symptom of the disease. It is rhythmic and alternating, at a rate of four to seven per second, and is seen most often in the upper extremities, usually in the distal portion. Tremor occurs most frequently in the flexors, extensors, pronators and supinators of the hand and in the flexors, extensors, adductors and abductors of the fingers. In the lower extremities the symptom is manifested as quivering of the knees and to-and-fro shaking of the feet. Tremor may be limited to one side of the body or to one extremity. It is present at rest but may be momentarily lost at the initiation of voluntary movement. In advanced cases tremor is present constantly.

Rigidity may be present in the musculature of the extremities, spine, head, neck or face. It may be associated with tremor or may exist independently. In those cases where rigidity exists without tremor, that symptom alone may be very disabling; in some cases effective voluntary movement is almost impossible. Another manifestation of rigidity is the "masklike" facies. Facial expression is slight and the normal movements of facial muscles associated with emotion are not seen. There may be marked slowness in movement. Initiation of movement is often difficult; once the movement has been started, it may progress smoothly. This symptom is usually associated with muscular rigidity.

Electromyographic studies have been reported by Hoefer and Putnam[1] in cases of paralysis agitans. It was noted that Parkinsonian rigidity is characterized by a continuous, slight innervation of the rigid muscles even when the limb is placed in its most relaxed position; rigidity thus results from simultaneous innervation of agonist and antagonist muscles at an average rate of 5.5 per second. The rate is surprisingly constant over a long period of time.

The course of the disease is in most cases progressive. Tremor and rigidity increase in severity producing acute discomfort and pain. This is associated with progressive incapacity; ultimately the patient can do very little for himself, requiring constant care.

When the disease has reached a moderately advanced stage, the patient must usually give up his work and find financial support in his family or community. The victim also becomes increasingly dependent

on his family for physical assistance and companionship. Visitors are often not encouraged to come, because of the embarrassment that is felt in their presence. Relations within the family become strained because of the irritability of the patient, and the inconvenience and deprivation imposed on the family by this chronic illness. Ultimately, the patient may reach a state of physical and financial helplessness, social isolation and great emotional disturbance.

Medical Therapy

Many drugs have been tested and used in the treatment of Parkinsonism. For many years the atropine series of drugs including hyoscine hydrobromide, stramonium, atropine and Bulgarian belladonna were the basis of medical treatment. Within the last few years, however, there has been an increasing interest in new medications.

In 1941 Bennett[2] suggested that the relaxant action of curare might be of value in the treatment of tremor and rigidity. D-tubocurarine suspended in peanut oil and wax was tested by Bird and Meyers[3] and reported in 1949 to be without value. Tolserol, a related drug, has likewise been used without benefit. The use of parpanit has been reported by European observers; the results have not been good. Diparcol, a synthetic muscle relaxant, has been evaluated by Duff,[4] who found some improvement in a series of eight cases, although one death which may have been related was reported. Other investigators have reported a mortality of 5 per cent in cases treated with diparcol. Lysivane, a member of the same series of drugs as diparcol, has been tested in sixteen cases by Palmer and Gallagher,[5] who reported improvement in some of their cases; there were no deaths in this series.

Artane, a synthetic chemical with anti-spasmodic effect, has been used by Doshay and Constable.[6] The drug was found to provide symptomatic relief comparable to or greater than that afforded by the belladonna alkaloids with fewer toxic reactions. Rigidity and tremor appear to be improved in the majority of patients, with greater relief of rigidity.

Anti-histaminics, including benadryl, pyribenzamine, histadyl and thephorin, have also been tested. Denker and Effron[7] reported on the use of benadryl in 46 patients with improvement in 76 per cent of the cases. Benadryl and hyoscine hydrobromide were found to be more effective in combination than either drug alone. Pyribenzamine and histadyl were comparatively ineffective in the great majority of cases.

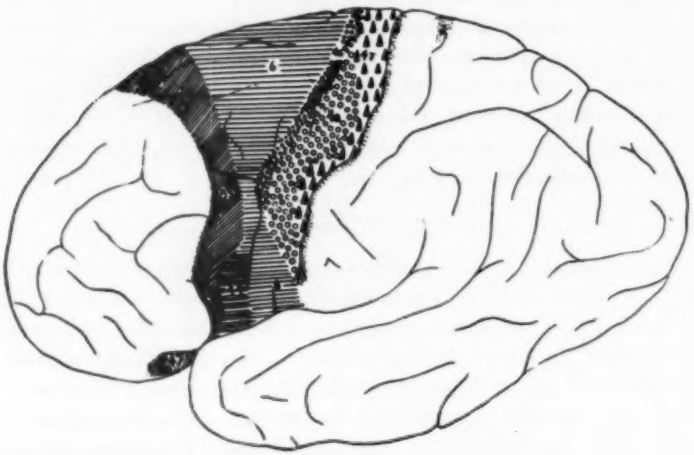

Figure 1—The human precentral motor cortex (areas 4$_\gamma$, 4a, 4s, 6 and 44) and some adjacent areas. (From Bucy, P. C. Surgical relief of tremor at rest, Am. Surg., 1945, 122:933.)

The new drugs, such as artane and benadryl, probably are an improvement over the atropine series of drugs in the treatment of the symptoms of Parkinsonism. However, at best there is only an amelioration of symptoms; the course of the disease is not checked. In most cases of moderate and severe involvement, drug therapy to date is only of slight benefit.

Surgical Procedures

The surgical procedures in use at present may be divided into three groups on the basis of anatomic level of approach: 1) Cerebral cortex, 2) Basal ganglia, 3) Spinal cord.

Studies of the details of cortical structure have revealed that the human brain contains several hundred areas, differently constructed; these may be grouped into a few regions corresponding to the lobes. Brodmann's numerical designation of the principal fields has been adopted for descriptive purposes. In a consideration of cortical procedures for relief of symptoms of Parkinsonism, interest centers on the motor area, area 4, which lies in the precentral convolution, and the

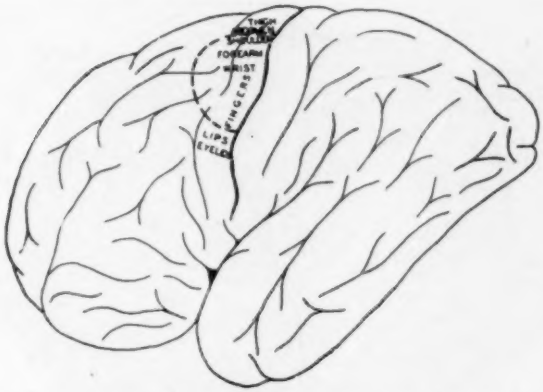

Figure 2—Schematic drawing in case of excision of areas 4 and 6 by Bucy and Case, showing motor representation of various parts of the right side of the body in the precentral gyrus as determined by electrical stimulation. The area of cortex excised is outlined by a broken line and includes all the representation of the upper extremity. (From Bucy, P. C. and Case, T. J. Tremor: physiologic mechanism and abolition by surgical means, Arch. Neurol. & Psychiat., 1939, 41:721.)

premotor area, area 6, which lies in the anterior part of the precentral convolution and the posterior part of the superior and middle frontal convolutions.

In a consideration of spinal cord procedures, interest centers on the pyramidal and extrapyramidal pathways into which all motor tracts may be divided. The pyramidal group includes the lateral and ventral pyramidal tracts. The extrapyramidal group includes the rubrospinal, vestibulospinal, tectospinal, reticulospinal, mesencephalospinal and olivospinal tracts; of these, the rubrospinal and vestibulospinal are probably the most imporant.

The cortical procedures are in part based on the observation of Parkinson[8] in 1817 that in one of his cases generalized tremor at rest was abolished on the right side during the time that the side was paralyzed as the result of a cerebral vascular accident. Parkinson stated: "During the time of their having remained in this state, neither the arm nor the leg of the paralytic side was in the least affected with tremulous agitation; but as their paralyzed state was removed, the shaking was returned."

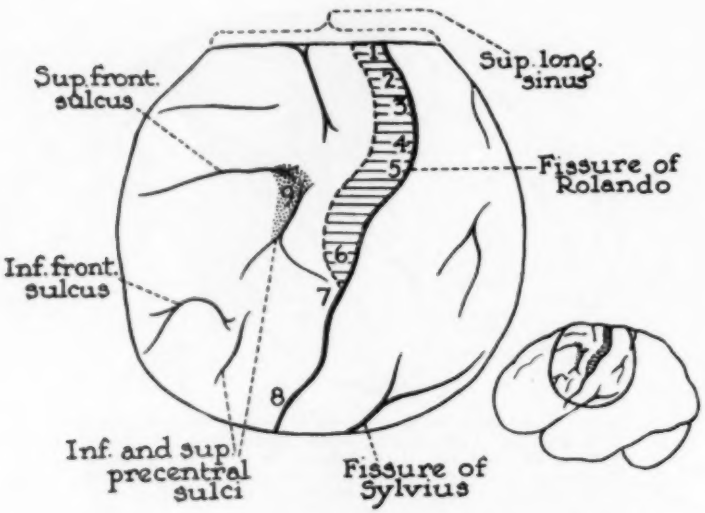

Figure 3—Artist's sketch of the cerebral cortex exposed at operation by Bucy in case of excision of area 4γ. The inset indicates the general relation of the exposed cerebral cortex. The numbers designate areas of various response to electrical stimulation The area for flexion of right hip is indicated by 1; for contraction of right quadriceps femoris muscle by 2; for contraction of right pectoralis major muscle by 3; for flexion of fingers of the right hand by 4; for flexion of the right elbow and wrist by 5; for movement of the neck and shoulder by 6; for movement of the right corner of the mouth and contraction of the right platysma myoides muscle by 7; for movement of the lower lip by 8; the suppressor area, 4s, is designated by 9. The area which was extirpated has been indicated by cross-hatching. (From Bucy, P. C. Surgical relief of tremor at rest, Ann. Surg., 1945, 122:933.)

This observation was confirmed by Patrick and Levy[9] in 1927, who reported a case of bilateral parkinsonian tremor in which, fourteen months after the onset of tremor, a right hemiplegia developed. With the onset of paralysis the tremor disappeared on the right side but gradually returned as the patient recovered the use of his right arm. Fulton, Liddell and Rioch[10] demonstrated that removal of the cerebellum in the cat resulted in a tremor of the extremities that appeared only on voluntary movement, i. e., an intention tremor. They observed that tremor in the contralateral extremities was abolished by removal of one cerebral hemisphere. Aring and Fulton[11] have shown in work on monkeys and baboons that intention tremor resulting from a cerebellar lesion is tem-

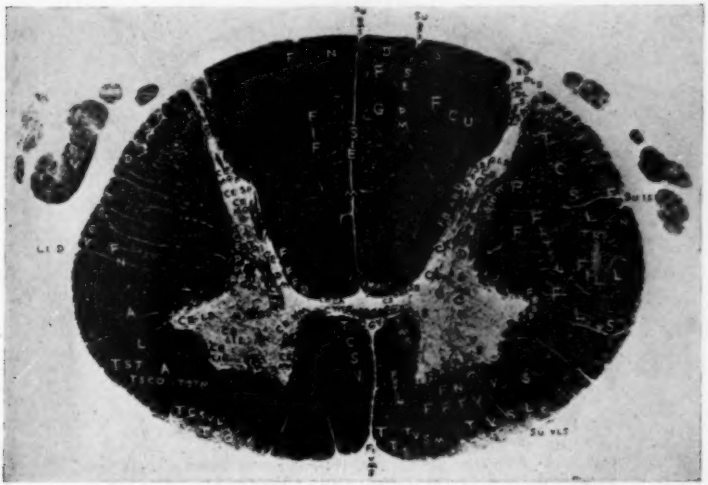

Figure 4—Cross-section of the spinal cord at the level of the fifth cervical segment. FCU, fasciculus cuneatus; FG, fasciculus gracilis; FRTSL, lateral reticulospinal tract; FRTSM, medial reticulospinal tract; TCSL, lateral corticospinal tract; TCSV, ventral corticospinal tract; TCSVL, ventrolateral corticospinal tract; TMS, mesencephalospinal tract; TRS, rubrospinal tract; TSCD, dorsal spinocerebellar tract; TSCO, spinocollicular tract; TSCV, ventral spinocerebellar tract; TSO, spino-olivary tract; TST, lateral spinothalamic tract; TSTM, medial spinothalamic tract; TTS, tectospinal tract; TVSL, lateral vestibulospinal tract; TVSM, medial vestibulospinal tract. (From Riley, H. A. An atlas of the basal ganglia, brain stem and spinal cord, Baltimore, Williams and Wilkins, 1943.)

porarily abolished and subsequently diminished by extirpation of area 4, is accentuated by extirpation of area 6, and permanently disappears after removal of areas 4 and 6.

These data were applied clinically by Bucy and Case[12] in 1939 in the case of a man, thirty-three years old, who had sustained a severe cerebral injury which was followed by a right hemiparesis and a coarse tremor, which was marked in the right upper extremity and slight in the right lower. Tremor was present at rest and in association with voluntary muscular activity. Hyoscine hydrobromide, phenobarbital and bulbocapnine had failed to influence the tremor. A left osteoplastic flap was reflected, centered on the precentral gyrus. Anesthesia was lightened and the cortex stimulated with a faradic current, using a unipolar electrode. The region of representation of the right shoulder, forearm,

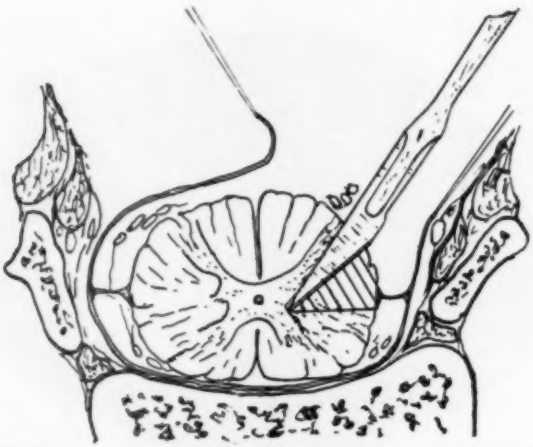

Figure 5—Diagram of the technique of section of the lateral pyramidal tract in the spinal cord, as performed by Putnam. (From Putnam, T. J. Operative treatment of the dyskinesias, A. Research Nerv. & Mental Dis., Proc., 1942, 21:666.)

wrist and fingers in areas 4 and 6 of the precentral gyrus was outlined. This segment was extirpated. It included the anterior wall of the Rolandic fissure down to its very bottom, and extended forward to include the posterior part of the neighboring frontal convolutions. The entire thickness of the cortex and some of the immediately subjacent white matter was removed, producing a defect 2.3 by 3.5 cm. on the surface; its greatest depth, 1.5 cm., was at the Rolandic fissure. The "face" area was spared. Following operation it was noted that there was a complete right hemiplegia. The paralysis of the face and lower extremity soon disappeared almost entirely. In the upper extremity there was moderate return of function, but movements were slow and awkward; discrete fine movements of the hand and fingers did not return. Of great interest was the fact that tremor both at rest and on voluntary movement completely disappeared and was still absent fifteen months after operation.

In 1940 Putnam[13] reported his experiences with cortical excision for the relief of unilateral tremor. The first case was that of a policeman, aged twenty-nine, who had been thrown from a motorcycle striking his

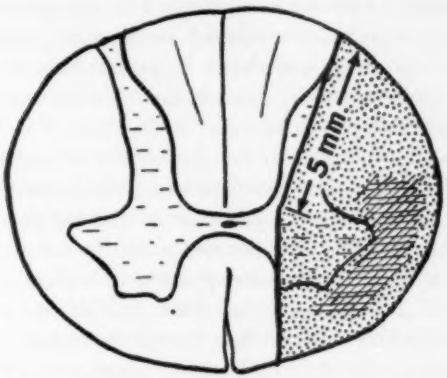

Figure 6—Sketch illustrating complete section of the lateral column of the spinal cord, as performed by Oliver. (From Oliver, L. C. Surgery in Parkinson's disease: complete section of the lateral column of the spinal cord for tremor, Lancet, 1950, 1:847.)

head against the ground. Three weeks later his left hand and arm began to tremble to a degree which forced him to give up active duty and become a police photographer. Examination disclosed an alternating tremor at rest in the left forearm and hand which was diminished by voluntary movement. The tremor was sufficiently troublesome so that the patient was willing to undergo surgical treatment. A right fronto-parietal flap was turned adjacent to the superior longitudinal sinus. Face, hand and arm areas were identified by means of a current from an induction coil just strong enough to produce contraction of the temporal muscle. The area corresponding to the arm was found at the vertex; the leg region could not be reached, presumably lying on the medial surface of the hemisphere against the falx cerebri. Firm pressure was exerted with a spatula on the precentral convolution. After three seconds the patient stated that his arm felt weak, and simultaneously the tremor stopped; 2 cc. of procaine hydrochloride was injected into the region and the tremor remained arrested. After waiting ten minutes the strip of cortex was resected by means of the cutting current. It measured 2.5 cm. in length, 1 cm. in width and 1.8 cm. in depth, including a small amount of white matter. After operation there was noted a flaccid monoplegia, affecting the left arm, without sensory changes, which

gradually improved over the next month. Four months after operation there was little weakness but marked awkwardness of the hand and arm. Tremor was almost completely abolished. Microscopic study of the block of tissue removed indicated that it had been taken from area 6 and a small adjacent part of area 4.

The second case reported by Putnam was that of a 45 year old woman who had suffered an acute febrile illness of short duration which was followed by the appearance of tremor of the left upper and lower extremities. An operative exposure similar to that used in the first case was made. A block of cortex corresponding to the arm area measuring 2 cm. in length, .4 cm. in width and .6 cm. in depth was excised. Immediately after operation there was a flaccid monoplegia and complete absence of tremor. Seven months after operation moderately severe weakness of the left hand existed. Tremor at rest was abolished and there was only slight tremor on movement. Examination of the block of excised tissue indicated that it came entirely from area 6.

Klemme[14] has had a wide experience with cortical excision in the treatment of paralysis agitans and athetosis. However, he has never reported the details of the operative procedure other than that it involves "premotor cortical excision." In a letter to Putnam[13] he indicated that the extirpation was in the frontal region anterior to the electrically excitable cortex, suggesting excision of area 6. He bases his operation on the contention that there is a balanced functional relation between the premotor cortex and the basal ganglia, transmitted by a premotor corticospinal "bundle" to the ventral horn cells of the cord. He believes that in Parkinsonism this balance is destroyed by involvement of the basal ganglia, and that it is restored by excision of the premotor area.

Reid, [15] in 1948, reported on a series of 15 cases in which area 6 alone, and area 6 plus a small part of area 8, were removed. In this work an osteoplastic flap was turned down under local anesthesia to expose areas 4, 4s, 6 and 8. Area 4 was mapped out by bipolar stimulation, using a special thyratron spike-wave stimulator, at frequencies of 60 and 80 cycles per second with an output of 6 to 8 volts. Electrographic tracings were made directly from the cerebral cortex to locate the anterior suppressor strip, area 4s. Stimulation is carried out in front of the previously localized motor points in order to identify area 4s. If stimulation of a particular point abolishes the tremor and spontaneous electrical activity in the cortex for about 90 seconds, that point is regarded as being within

the suppressor strip, area 4s. This region is considered the posterior limit of the segment to be removed. All areas containing points identified as belonging to areas 4 and 4s are carefully preserved. The whole precentral convolution is thus left intact. The tissue immediately anterior to the precentral convolution is removed by careful subpial resection. Although it is possible that a small part of area 6 may be left behind by this method, it has been adopted to avoid as far as possible interference with the blood supply to areas 4 and 4s, thereby minimizing the chance of postoperative loss of motor power, or of impairment of suppressor effects of area 4s. It is believed that the continued activity of area 4s is an essential part of the postoperative result. The remaining three borders of the area removed are mapped out by anatomical inspection. The lower limit of removal corresponds to the level of the face area in area 4, except on the side of the motor speech area, in which the resection is not extended below the level of the arm area. The medial boundary of resection is the midline. The anterior boundary is gauged on morphological grounds, being as far as one can judge the junction between areas 6 and 8. It is not known what the result of removing all of area 8 would be, but in several of the late cases the anterior limit of resection was extended more and more forward into area 8 with more encouraging results.

In 1945 Bucy[16] reported on a further development of his work in the surgical treatment of tremor. After considerable research into the anatomy and physiology of the precentral cortex, he came to the conclusion that the impulses transmitting tremor travel specifically in the posterior part of the precentral gyrus, in area 4γ; the Betz cells, from which the large fibers of the pyramidal tract arise, are located in this strip. If this were true, cortical extirpation could be restricted to the posterior part of the precentral gyrus; areas 4a, 4s and 6 could be preserved. It seemed likely that such a limited excision would result in less paralysis than that which follows the larger removal of areas 4 and 6. The case of a young man, aged 23, who had suffered since the age of 8 from tremor at rest and mild spastic hemiparesis affecting the right extremities appeared suitable for trial. An osteoplastic flap was reflected under local anesthesia in the left fronto-parietal region, centered on the Rolandic fissure. The exposed cortex was carefully stimulated with a 60 cycle sine wave current, using a bipolar electrode. Motor responses were obtained only from the posterior part of the precentral gyrus.

The posterior half of the precentral gyrus, in those regions from which movements of the right upper and lower extremities were produced, was then removed subpially down to the bottom of the Rolandic fissure. Nine months after operation examination revealed complete absence of tremor. There was however considerable additional paralysis of the right upper extremity and some increase in spasticity.

Meyers[17] has done considerable work in surgery of the basal ganglia for treatment of tremor. His procedures involved extirpation of the head of the caudate nucleus and interruption of certain extrapyramidal fibers in the region of the anterior limb of the internal capsule.

Insofar as surgery of the spinal cord is concerned, numerous abortive efforts were made to relieve the symptoms of Parkinsonism. Pollock and Davis[18] cut several posterior roots in a case of rigidity and tremor affecting one upper extremity. Rigidity was diminished but not tremor. The column of Burdach was cut by Puusepp[19] with decrease in rigidity but not in tremor. The antero-lateral column was cut by Foerster and Gagel[20] without producing any change in symptoms. Putnam[21] performed antero-lateral cordotomy in five cases without success. Machansky[22] reported permanent recovery in three and satisfactory results in five of a series of seventeen patients subjected to cervical antero-lateral cordotomy. Oldberg[23] sectioned the antero-lateral column in two cases of unilateral tremor without effect.

It was not until 1940 that a substantial advance was made in spinal cord surgery for relief of tremor. Putnam[13] observed that section of the long descending extra-pyramidal tracts in the antero-lateral and anterior columns greatly decreased movements of an athetoid character but had no effect on alternating tremor. It therefore seemed reasonable to believe that, since impulses producing tremor must pass along some motor pathway, the lateral pyramidal tract was essential to the production of tremor. It had been observed by Rothmann[24] that section of the lateral pyramidal tract in monkeys produced little disability, so that there seemed reason to believe that it might be well tolerated in human beings. After some effort a case was found in which unilateral tremor was sufficiently incapacitating to justify the possible risks involved in cutting the pyramidal tract. The patient was a 32 year old woman who had had tremor of the right upper and lower extremities for sixteen years. Tremor was more severe in the upper than the lower extremities and interfered greatly with function. Under avertin anesthesia cervical

laminectomy was performed and the 4th cervical segment of the spinal cord was exposed. A #11 Bard-Parker blade was inserted into the lateral column adjacent to the point of exit of the posterior roots at an angle of 15 degrees to the vertical, to a depth of 4 mm. and then withdrawn. On the following day it was found that the left arm and leg were flaccid, and only the slightest movements of the fingers were possible. Strength rapidly returned so that on the 18th day the patient was able to walk and use her hand for drinking and writing. No tremor was observed at rest and only slight tremor was seen on movement. There was no increase in muscle tone. Four months after operation tremor at rest returned to about one-half its original intensity. A more radical operation was therefore decided upon. This time the point of the knife was swept out laterally to the horizontal meridian of the cord, thus transecting a triangular area just lateral to the posterior horn, measuring approximately 4 mm. along each side. One year after the second operation it was noted that the patient had about one-third the preoperative strength of the hand and arm. Gait was definitely hemiparetic, but the patient could walk better than after the first operation. No tremor at rest was seen, but slight tremor appeared on movement.

Oliver[25] in 1949 reported on a series of 48 cases in which a procedure slightly more radical than that described by Putnam was performed. The postero-lateral column was incised to a depth of 5 mm. as compared with 4 mm. in Putnam's original report. Oliver noted that the results were better in those patients who after operation had patches of analgesia on the opposite side resulting from involvement of the lateral spinothalamic tract.

In an attempt to improve the results, Oliver[26] increased the extent of incision in the cord to include the whole of the lateral column so that complete analgesia was produced on the opposite side to a level high up on the thorax, sometimes including the upper limb. Cervical laminectomy at the level of the second and third cervical vertebrae was performed. A #15 Bard-Parker blade was clamped with an artery forceps so that 5 mm. of the blade projected beyond the beak of the instrument. The blade was pushed into the cord at the site of attachment of a posterior rootlet at an angle of 45 degrees to a depth of 5 mm. The division of the lateral column was then completed with a blunt instrument which was inserted into the cord and brought forward to emerge at the line of attachment of the anterior nerve roots.

In 1946 the writer[27] became interested in the surgical treatment of the symptoms of Parkinsonism. It was naturally of the first importance to determine the neural pathways through which the impulses producing these disorders travel. It would then be possible to select the best surgical site to interrupt them.

On the basis of his experiences with excision of area 4γ and Putnam's results following section of the lateral pyramidal tract in the spinal cord, Bucy[16] had suggested that tremor is transmitted from the Betz cells of area 4γ through the large fibers of the pyramidal tract, and that destruction of the substantia nigra or the globus pallidus or of both is the commonest lesion which releases the pyramidal system to this form of abnormal hyperactivity.

Area 4 in man is divisible into three parts, 4γ, 4a and 4s, all of which probably contribute to the pyramidal tract. The human pyramid just rostral to the decussation contains roughly about a million nerve fibers, of which 61 per cent are myelinated and the rest unmyelinated. Of the myelinated fibers, 90 per cent are 1 to 4 microns, approximately 7 per cent are 5 to 9 microns and approximately 2 to 3 per cent are more than 9 microns in diameter. It is from the large Betz cells of area 4γ that the large pyramidal fibers greater than 9 microns arise. The remaining fibers that make up the pyramidal pathways are believed to arise from areas 4a, 4s, from an indefinite portion of the parietal lobe and possibly from area 6.

The pyramidal pathways in man consist of a large crossed lateral bundle, the lateral corticospinal tract, a small uncrossed lateral bundle, the ventrolateral corticospinal tract, and an extremely variable uncrossed anterior bundle, the ventral corticospinal tract. The degree of decussation is more variable in the human brain than in the brain of other primates. Flechsig in 1876 found in his series of human brains some with large lateral and negligible ventral pyramidal tracts and others with large ventral and small lateral tracts.

The lateral corticospinal pathway runs the length of the cord and the ventrolateral corticospinal pathway may. The ventral corticospinal tract is believed to terminate in the thoracic region, although at times it may be traced to the lower lumbar region. The lateral pathway ends in the anterior gray column of the same side, whereas the ventrolateral and ventral tracts cross to the gray column of the opposite side.

It seemed possible that the difference in the results following Bucy's

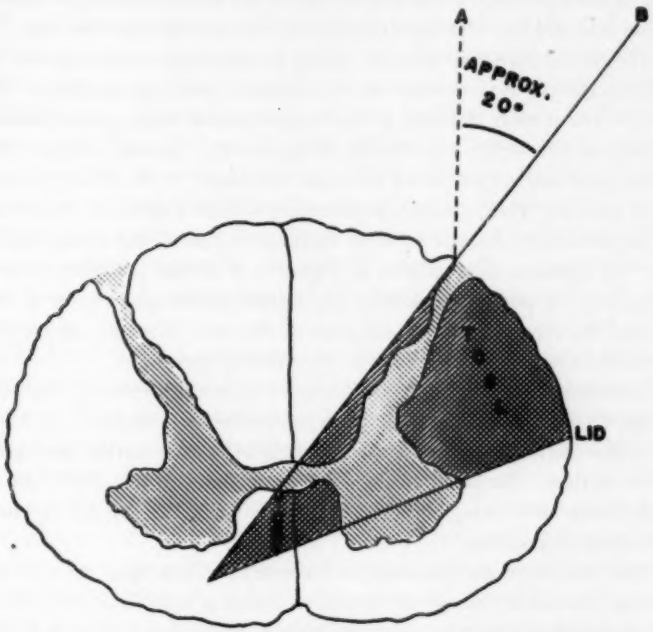

Figure 7—Diagram illustrating technique of combined lateral and ventral pyramidotomy. TCSL, lateral corticospinal tract; TCSV, ventral corticospinal tract; LID, dentate ligament; B, line of incision, at angle of approximately 20 degrees with the vertical, A, depth of incision, 8 to 9 mm. (From Ebin, J. Combined lateral and ventral pyramidotomy in the treatment of paralysis agitans, Arch. Neurol. & Psychiat, 1949, 62:27.)

section of area 4γ, in which case there was complete cessation of tremor, and Putnam's section of the lateral pyramidal tract, in which case there was partial relief of tremor, might possibly be attributed to the fact that lateral pyramidotomy does not interrupt all the fibers arising from the large Betz cells of area 4γ. It seemed possible that more complete relief of tremor by the spinal cord approach might be achieved by section of the ventral corticospinal pathway in addition to section of the lateral corticospinal. In view of the fact that at the level of the upper cervical portion of the cord the lateral pyramidal tract has already made its crossing and the ventral corticospinal pathway has yet to do so, the

contemplated procedure entailed section of the lateral corticospinal tract on one side and the ventral corticospinal tract on the opposite side.

The lateral corticospinal tract, lying in the posterolateral column, is easily sectioned. Interruption of the ventral corticospinal tract of the opposite side is more difficult, in view of its position in the posteromedial portion of the anterior column, alongside the anterior sulcus. The ventral tract might be reached in one of two ways: 1) By direct incision of the anterior white column, a procedure which is difficult and which would necessarily destroy most of its other tracts; 2) By cross incision from the opposite side, as seen in Figure 7, with the advantage that it would thus be possible to section the lateral corticospinal tract of one side and the ventral corticospinal tract of the other through one incision with relatively little unnecessary interruption of pathways.

Examination of specimens of the upper cervical portion of the cord indicated that this section could be accomplished by insertion of a blade in the line of the posterior roots at an angle of approximately 20 degrees to the vertical. The required depth of incision was 8 to 9 mm., the tip of the blade then being withdrawn in the line of the dentate ligament on the side of insertion.

The procedure was first used in the case of a man, aged 29, who had had encephalitis at the age of 10 years. This was associated with weakness and awkwardness of the right hand, which was followed shortly by the appearance of tremor and rigidity in the right upper and lower extremities. With the passage of time, shortening of the right upper and lower extremities became apparent. Of interest in the physical examination was the shortening of the right extremities. Neurologic examination disclosed right hemiplegic gait and coarse, rapid, alternating tremor of the right extremities, more pronounced in the upper. Tremor of the upper extremity was so severe that the patient found it necessary to sit on the hand and forearm to control it. Strength in the right extremities was almost normal except for the hand and fingers which could not be used because of flexion contractures. Muscle tone in the right extremities was greatly increased. Paralysis of the left oculomotor nerve was noted.

The operation was performed under local anesthesia so that tremor, rigidity and voluntary movement could be used to determine the proper extent of incision. Tremor was not reduced by preoperative medication, being strong enough to shake the operating table. Laminectomy of the 2nd, 3rd and 4th cervical vertebrae was performend. The dura was

opened to the right of the midline. The cord level between the 4th and 5th cervical segments was selected for incision so that there might be no interference with the function of the phrenic nerve which receives its main innervation from the 4th cervical segment. The posterolateral column on the right side was incised to a depth of 4 mm., sufficient to interrupt the lateral pyramidal tract, without abolishing tremor, rigidity or voluntary movement. A cataract knife was then inserted into the cord in the line of the posterior roots at an angle of 20 degrees to the vertical to a depth of 8 mm., and then drawn out at the dentate ligament. There was immediate cessation of the violent tremor in the upper and lower extremities on the right side and complete, flaccid paralysis of these extremities.

Bladder control appeared on the third day. Motor power began to return on the sixth day. The patient was able to walk at the time of his discharge from the hospital, two and one-half weeks after operation. Motor power reached its maximum in approximately three months. After twenty months it was observed that tremor at rest was absent except under the influence of extreme emotion. Tremor on movement was present but was much less severe than that noted preoperatively. Muscle tone in the right upper and lower extremities was almost normal. Muscle strength in the right lower extremity was the same as that observed before operation; in the right upper extremity motor power had returned to 90 per cent of its preoperative level. The patient was then doing manual labor.

This experience was of interest as it demonstrated the following points:

(1) Section of the lateral pyramidal tract alone does not immediately eliminate tremor, rigidity and voluntary movement.

(2) Cordotomy for section of the lateral pyramidal and the opposite ventral pyramidal tracts results in immediate disappearance of tremor, rigidity and voluntary movement.

(3) The procedure in this case produced great relief of tremor and rigidity, without regression, over a considerable length of time.

It was hoped that these results could be approximated in similar cases. The procedure was subsequently performed in 25 additional cases.

Postoperative Course—Urinary retention appears immediately after operation. Tidal drainage is therefore instituted on the patient's return from the operating room. Normal bladder control, appeared, on the

average, on the fifth or sixth day. Bowel function is aided by cathartics and enemas. The usual care of the skin is provided.

Paralysis has lasted on the average from eight to ten days, after which time there is gradual return of function. Function may return first in either the upper or the lower extremity, proximally or distally. Physical therapy which is begun on the fifth day includes heat, massage, passive and active exercises, reëducational exercises and sine wave stimulation. The patient is out of bed in a chair on the fourteenth day and is then gradually encouraged to stand and walk. The average period of hospitalization has been four weeks. Physical therapy is continued for five months after operation, treatments being given four times weekly.

Complications—(1) In two cases the postoperative course was stormy. In the first patient, who presented bilateral tremor, quadriparesis appeared on the second postoperative day. This was associated with severe cystitis and pyelitis which cleared up with urologic care. Hospitalization was extended for almost two months. At the time of discharge, the patient was able to walk with help and had moderate use of the upper extremities; return of function was greater on the side opposite to operation. Tremor was absent bilaterally. This patient was able for a time to get about and superintend the workings of his farm. However he is now bedridden with recurring bouts of pyelitis.

In the second patient quadriparesis also appeared on the second postoperative day. Severe cystitis and pyelitis were also associated with this complication. The infection ultimately responded to drug therapy. The patient was hospitalized for two months at the end of which there was only slight return of function.

(2) There were several cases of mild bladder infection which responded readily to treatment with drugs.

(3) Pain in the back of the neck, shoulder or arm lasting from several days to several months was a frequent complaint. In two cases this symptom was severe; burning pain was noted in the arm and forearm. It was thought that pain might have been due to damage inadvertently done to posterior rootlets. In subsequent cases particular care was taken to avoid these structures. Nonetheless, the symptoms continued to appear. They may be the result of damage within the cord to nerve fibers of the posterior root, or to the cells of the gray column.

(4) In eight cases there was difficulty in holding the head erect. It tended to be drawn toward the unoperated side.

(5) Pain and temperature sensibility was lost on the opposite side, usually in the lower extremity. In some cases it cleared up after several months; in others the loss was permanent. This was of course the result of section of some of the fibers of the lateral spinothalamic tract.

(6) A psychiatric reaction characterized by negativism was observed in one case.

(7) There was one postoperative wound hemorrhage which was satisfactorily cared for.

Results

Bucy and Case[12] have reported on the results of excision of areas 4 and 6 in several cases. Tremor was said to be completely abolished in each case and the motor function of the involved extremities was only slightly reduced. Putnam[13] reported on two cases of cortical excision of area 6. In one case tremor was markedly reduced, but motor function was also impaired to a marked degree. In the second case tremor was only slightly reduced and usefulness of the extremity was much impaired. Bucy[16] reported on excision of area 4γ. There was complete absence of tremor, but considerable additional paralysis of the upper extremity and some increase in spasticity. The results of Klemme[14] are difficult to evaluate.

Reid[15] has described his experiences with 15 cases in which area 6, and in some cases part of area 8, were removed. The response of tremor to the operation was problematical and inconsistent. In some cases relief was almost complete; in the majority it was somewhat reduced, but it was not abolished in any. He felt that increased muscle tone was generally reduced and that fine movements were more readily performed.

In the series of cases reported by Meyers,[17] in which the head of the caudate nucleus was resected and certain extrapyramidal fibers in the region of the anterior limb of the internal capsule were sectioned, the results have been equivocal. Tremor was completely relieved in several cases but not in others. In the series of cases in which section of the lateral pyramidal tract had been performed by Putnam,[13] there was substantial decrease in tremor. Function of the upper extremity was improved in all. Walking was better in some.

Oliver[25] reported on 48 cases of lateral pyramidal tract section. There was a mortality rate of 6 per cent with 3 deaths. Tremor was completely abolished in 12 per cent, reduced to a negligible degree in

37 per cent, unchanged in 12 per cent, and worse in 12 per cent. Usefulness of the arm was improved in 43 per cent, was unchanged in 23 per cent and was worse in 27 per cent. Walking was improved in 25 per cent, was unchanged in 33 per cent and was worse in 35 per cent; 54 per cent considered the operation worthwhile.

Oliver[26] subsequently reported his results following section of the lateral column, anterolateral as well as posterolateral. The operation was performed on 18 patients. With one exception, all of these patients were pleased with the result and were free of tremor except sometimes during moments of excitement. There were no deaths in this series.

With the passage of time the results of new techniques are seen in better perspective. Bucy[28] has more recently indicated that the results of cortical excision have not been satisfactory to him. Meyers' work on the basal ganglia has been of great interest from an investigative point of view. It seems questionable whether the procedures are of therapeutic value in cases of paralysis agitans. In so far as spinal cord procedures are concerned, several years ago Putnam[29] wrote that he was no longer performing lateral pyramidal tract section. Oliver[30] has recently indicated that he regarded surgery of the spinal cord as a last resort, to be used only when the patient was insistent in demanding relief of severe tremor.

At this point the results of cordotomy for section of the lateral and ventral pyramidal tracts, performed in 26 cases, will be reported. The follow-up period ranges from 7 months to 4 years. The results follow:

(1) There were 2 deaths in the series, a man of 22 and a woman of 69. In each case death occurred three months after operation. The patients were from out of town and had returned home six weeks after operation. The cause of death is not known in either case.

(2) Tremor was a prominent symptom in 23 cases. It was greatly reduced in 19 cases (82 per cent) and moderately reduced in 4 cases (18 per cent). The usual result was absence of tremor at rest, and slight or moderate tremor on movement or stress. There was no case in which tremor was not relieved.

(3) Rigidity was a prominent symptom in 8 cases before operation. After operation it was reduced in 4 and unchanged in 4. In 4 others, who had not been troubled with the symptom, increased muscle tone resulted from the operation.

(4) Muscle strength was diminished in all cases on the side of

operation. However, as tremor was relieved, the total function of the extremity was in some cases increased. In the upper extremity 7 (27 per cent) showed improvement, 12 (46 per cent) were unchanged and 7 (27 per cent) were worse. In walking, 2 (8 per cent) were improved, 12 (46 per cent) were unchanged and 12 (46 per cent) were worse.

It was observed that the personality make-up of the patient was of great importance in determining the final outcome. Since it is obviously not possible to restore the patient to a completely normal condition and since damage must be done to nervous tissue if tremor is to be relieved, the patient must adjust to a situation which is less than ideal. Patients of irritable, gloomy temperament found fault with even good results. Those of more sanguine, optimistic nature were pleased with results that were objectively less satisfying.

The over-all results of combined lateral and ventral pyramidotomy in which improvement is considered in terms of relief of symptoms, retention of moderate function and absence of complications of surgery follow:

Deaths	2	7.6%	
Improved			
Greatly	3	11.5%	
Moderately	4	15.4%	
Slightly	3	11.5%	38.4%
Unchanged	7	26.9%	
Worse	7	26.9%	

Study of the results in this group of cases suggests that the proper indications for cordotomy for section of the lateral and ventral pyramidal tracts in the treatment of Parkinsonism are the following:

(1) Relief of tremor is the only symptomatic indication. The results in cases presenting rigidity as the main symptom have been variable.

(2) Tremor must be severe and troublesome, without adequate response to thorough medical treatment. All drugs and combinations of drugs should be tested first.

(3) Cases with unilateral involvement are to be preferred.

(4) Cases with bilateral involvement, in which tremor is severe on only one side, may be considered.

(5) Personality of the patient should be optimistic, courageous and buoyant.

(6) Weight should be within average range. In obese patients too much weight must be borne by a weakened lower extremity. Walking has been more difficult in obese patients.

(7) Age should preferably be under 50.

(8) General physical condition should be good.

The results following combined lateral and ventral pyramidotomy have indicated that the chances of improvement are slightly better than 1 out of 3. In this group were a number of patients who do not meet what is now regarded as the proper indications for surgical therapy. If surgery is now limited to those who present these indications, the chances of improvement may be greater.

Pathophysiology

Prior to the investigations of the past fifteen years very little was known of the pathophysiologic mechanisms underlying the production and transmission of tremor and rigidity, the most prominent symptoms of Parkinsonism. The various surgical procedures performed for the relief of these symptoms have provided information which might be expected to shed light on their neural mechanisms and pathways.

In so far as rigidity is concerned, the mechanisms of production and the pathways of transmission are even at this time not definitely known. More is known about tremor.

The pathophysiology of tremor must be considered in two parts:

(1) How is it produced?

(2) Over which pathways is it transmitted?

In so far as the first part is concerned, there have been two prominent points of view. According to the "irritative" theory, tremor is the direct result of damage to nervous structures. According to the "release" theory, tremor is "released" by damage to an inhibiting neural mechanism. Bucy has supported the "release" theory. As noted earlier, he has suggested that tremor is transmitted from the Betz cells of area 4γ through the large fibers of the pyramidal tract. Bucy[31] has further suggested that the pyramidal system is released by interruption of an inhibiting mechanism which functions under normal circumstances. This circular inhibitory or suppressor mechanism is believed to originate in the precentral cortex, passing to the substantia nigra, to the globus pallidus, to the thalamus and back to the precentral cortex. Lesions of the substantia nigra, globus pallidus, or both, interrupt the suppressor mechan-

ism; the pyramidal system is released from control and tremor appears.

Study of the surgical experiences of the various workers in the field of surgical therapy of Parkinsonism reveals certain inconsistencies and contradictions. Bucy and Case removed areas 4 and 6 with permanent (4 year follow-up) abolition of tremor. Bucy has removed area 4γ with complete (9 month follow-up) relief of tremor. Reid has reported on excision of area 6 and part of area 8. In one case performed under local anesthesia, removal of a small portion of area 6 alone produced immediate cessation of tremor of the right hand, without impairment of voluntary movement. (Tremor gradually returned and after 18 months it had returned to the preoperative level.) Klemme, who has never published details of his technique, has excised cortical tissue anterior to the excitable motor cortex, which presumably included area 6 and perhaps area 8. Abolition of tremor has been reported in a high proportion of his cases; the writer has seen two of his patients who were almost entirely free of it. Thus, in the group of cortical procedures, excision of area 4γ has been reported to abolish tremor, as have excision of area 6, and excision of area 6 plus a small portion of area 8.

In the group of spinal cord procedures, Putnam had originally reported that section of the posterolateral column in the cervical region interrupting the lateral pyramidal tract caused great reduction in tremor. Oliver reported that in his hands more complete relief of tremor was provided by section of the anterolateral column and the lateral portion of the anterior column in addition to the posterolateral column. It is of interest that Putnam had observed earlier that extensive destruction of the anterolateral column and the lateral portion of the anterior column was of some value in the relief of athetosis, but was of no value in tremor. It was my experience that section of the lateral pyramidal tract did not provide satisfactory relief of tremor. Better results were obtained with the more extensive cordotomy interrupting among other tracts the lateral pyramidal and the opposite ventral.

Certain facts emerge from this group of experiences:

(1) It is not wise to attach too great significance to the results of surgical procedures on the human brain and spinal cord in attempting to work out precise details of pathophysiology. The procedures are gross; it is often not possible to be certain of topographical areas. This is particularly true of the cortex; in the living brain it is difficult to identify specific convolutions, and much more difficult to identify Brod-

mann architectonic areas. Furthermore, since deaths have fortunately been rare, it has not been possible to check on the precise location and extent of the incision or excision, which is always done in valid investigations in experimental animals.

(2) In so far as Bucy's theory regarding tremor is concerned, relief of tremor by excision of area 6, and by excision of areas 6 and 8, as well as by excision of area 4γ,—and the greater relief obtained in the spinal cord approach by extensive cordotomy than by lateral pyramidal tract section alone, suggest that the impulses transmitting tremor are not restricted to area 4γ and the pyramidal tract. It seems likely that these impulses actually pass or may potentially pass through all motor pathways, extrapyramidal as well as pyramidal.

The relief of tremor by cordotomy for interruption of the lateral and ventral pyramidal tracts is probably to be attributed to the fact that the incision interrupts all the pyramidal innervation to a side and also much of the extra-pyramidal, including the rubrospinal, lateral reticulospinal and mesencephalospinal tracts.

(3) As a corollary of (2), effective relief of tremor cannot be accomplished by surgery of the brain or spinal cord without at least moderate loss in motor power.

Future Therapy

At this point it might be of interest to consider what the future may hold in the treatment of Parkinsonism. As matters stand now, drug therapy can provide moderate relief for cases presenting slight involvement. Among the cases of moderate and severe involvement, which are only slightly benefited by even the new drugs, some will find relief in the surgical procedures that are known today. These will include cases of unilateral tremor, and occasional cases of bilateral tremor more severe on one side in people of well-integrated personality. However, many cases of moderate and severe involvement have at present no means of significant relief. From what direction may help for these cases come?

There are three possibilities:

(1) Prophylaxis—It is possible that advances in the understanding of virus and degenerative diseases may point out methods of preventing the development of the Parkinsonian syndrome. However, this does not appear likely in the near future.

(2) Drugs—This is an age of scientific marvels. It is possible that

new drugs will be developed which will control symptoms in even the most severe cases.

(3) Surgery—In so far as surgery of the nervous system for the relief of tremor and rigidity is concerned, it is almost certain that we have gone as far as we can go. Since it appears likely that the impulses mediating tremor may travel along all motor pathways, both pyramidal and extrapyramidal, it is improbable that a surgical procedure can be developed which will provide greater relief of tremor with less interference in function. Rigidity has not been consistently relieved by any of the surgical procedures used in Parkinsonism, even though the motor system has been thoroughly investigated.

In summary, the outlook for the treatment of cases of Parkinsonism with slight involvement is good; drugs are effective in this group. Certain selected patients with moderate and severe involvement in whom tremor is the main complaint may be benefited by surgery of the brain or spinal cord. However, for many patients in the last two groups there is at this time no effective treatment. Nonetheless, in view of the unprecedented activity in all fields of medicine and related science, the outlook is by no means without hope.

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BODY WATER IN MAN AND ITS SUBDIVISIONS*

J. MURRAY STEELE

KNOWLEDGE of the amount of water in the human body and of its distribution with respect to what part of the water is outside and what part is inside cells is a matter of considerable importance to medicine, surgery and physiology. The present study was stimulated chiefly by a desire to learn whether changes in water content occurred during the process of aging.

A measure of total body water in living man has long been sought. The first successful measurement was made in 1934 by von Hevesy and Hofer[1] who fed deuterium oxide to a man. By estimating the degree of dilution of deuterium oxide after sufficient time had been allowed for equilibrium to take place, it appeared that the man contained 62 per cent water. In 1947 Pace, Kline, Schachman and Harfenist,[2] using tritium oxide (radioactive water), obtained a figure for body water in one male of 63 per cent. Moore[3] in the same year arrived at a figure of 72 per cent in a single male subject to whom he administered deuterium oxide intravenously. In 1949 Hollander et al[4] measured body water by dilution of heavy water in two normal subjects. The figures were 54.9 and 58.5 per cent body weight.

Data available in this laboratory suggested that antipyrine, one of the early antipyretics which Dr. B. B. Brodie was studying, appeared to be equally distributed throughout body water. Further investigations in animals and finally in man were undertaken which showed that with minor exceptions, this was so.[5] The method of measurement of total body water with antipyrine was simple. A gram of the drug was injected intravenously. Since antipyrine is metabolized slowly in the body (average rate 6 per cent per hour), disappearance of the drug from the blood becomes logarithmic in nature, when equilibrium with body water is established. The time required for equilibrium to occur was approximately three hours in normal individuals and longer than five hours in edematous individuals. Three to four blood samples were

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analyzed.[6] The concentrations of antipyrine were plotted on the logarithmic scale of semi-logarithmic paper against time on the arithmetic scale and the resultant straight line was extrapolated back to the time of injection to obtain the concentration of antipyrine if equilibrium had been instantaneous. The amount of antipyrine given, divided by this concentration in plasma water, indicated the amount of water in which the antipyrine was dissolved—in this case, total body water.

The volume of dilution of antipyrine was compared with that of deuterium oxide by simultaneous measurements in eight normal individuals. The agreement was fairly good. Antipyrine space averaged 1.2 L. less than deuterium oxide; the greatest difference was 3.1 L. In desiccation experiments in rabbits in which antipyrine space was measured prior to sacrifice, agreement within 3 per cent was obtained.[7]

A metabolite of antipyrine, N-acetyl 4-amino-antipyrine (NAAP), also distributes evenly throughout the water of the various tissues of the body and is diluted to approximately the same extent in the body as antipyrine. Simultaneous measurements of antipyrine and NAAP spaces in twelve normal subjects agreed fairly well. The average volume of dilution of the NAAP was, however, 1.8 L. (6 per cent) less than antipyrine.[8] There are, then, three substances, deuterium oxide, antipyrine and one of its metabolites, which are distributed evenly throughout tissue water and are diluted to the same degree in the body.

Measurement of specific gravity of the body also yields information as to the amount of water in the body, as Behnke and his group have shown.[9] The body can be regarded as composed of a mixture of fat of low density and fat-free tissue of relatively high density. From the specific gravity of the body as a whole the proportion of either fat or fat-free tissue may then be calculated. The sum of all the fat-free tissues has been regarded by Behnke as "lean body mass." The lean body mass was shown by Behnke's studies and later by Pace and Rathbun[10] to exhibit considerable constancy as to the water content, namely, 73 per cent. These authors also reviewed the literature which tended to show that the figure is a fairly constant one for a number of mammalian species.

Hastings[11] has emphasized the fact that only when tissues free of fat are considered, can reliable data on the relative composition of the tissues as to water and electrolyte content be obtained. From data on the specific gravity of the body Behnke[9] has shown that what is true for the individual tissues of the body is more or less true for the body as a whole.

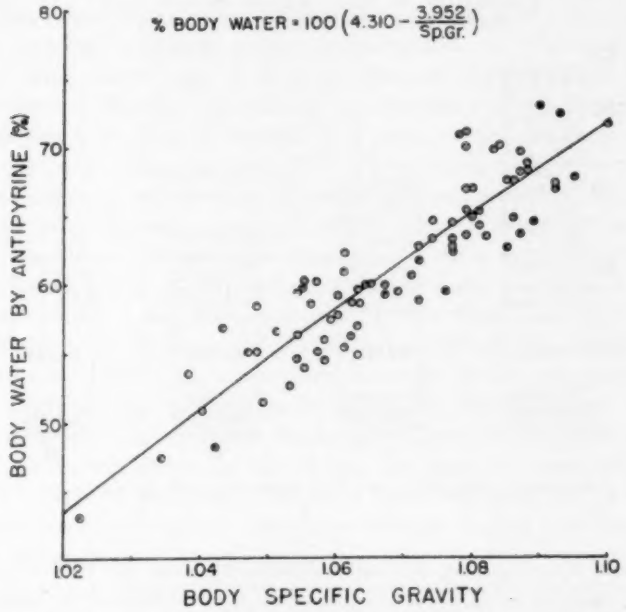

Fig. 1. (From Osserman, Pitts, Welham and Behnke[13]). The relationship between specific gravity of the body and water content. (Coefficient of correlation r = 0.90).

In this laboratory the water content was calculated from specific gravity and from dilution of antipyrine in nine subjects.[12] The agreement was fairly good. Calculation of the water content of "lean body mass" from the antipyrine figure affirmed the constancy of the proportion of water in lean body mass, yielding an average figure of 71.8 per cent.

Osserman, Pitts, Welham and Behnke[13] extended measurements of specific gravity and antipyrine space to a large number of young men, eighty-one in all. The correlation of specific gravity and proportion of water was excellent (Fig. 1). The more obese individuals of low specific gravity had, of course, proportionately less water. Recently, additional confirmation of the validity of both specific gravity and antipyrine dilution as measures of body water in cattle, has been

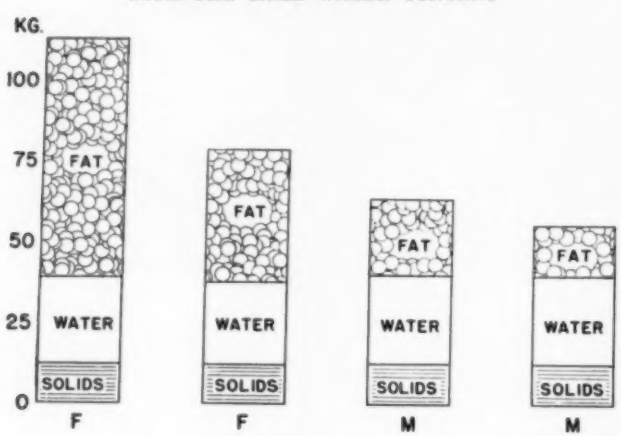

Fig. 2. Individuals with similar lean body masses but with variable stores of fat.

obtained by comparing the values obtained by these two methods with those obtained by an extraction procedure after sacrifice of the animal.[14] That fat is the great variable in body composition is illustrated by four individuals chosen from the group of subjects studied in our laboratory because their lean body masses were the same (39 to 41 K.) but those whose body weight varied from 60 to 106 K. (Fig. 2).

Thus the amount of water in the body estimated by methods based on the dilution of chemical substances agrees well with the amount estimated by a method based on an entirely different principle, namely, on the measurement of specific gravity of the body. That these divergent procedures agree well lends confidence to the belief that any one of them is a measure of total body water within the limits of error of the method chosen.

The reproducibility and limits of error of the antipyrine dilution were tested in three subjects measured on four separate occasions. Maximum deviation from the mean was 2 to 3 L. or 5 to 8 per cent.[15] With errors of this magnitude, even though percentagewise they are small, it is clear that changes in the state of hydration cannot ordinarily be measured unless they are very large. A significant change in degree

of dehydration might take place before it could be detected.

The results of the use of this method are easy to state. Body water was measured in hospital patients and personnel. In fifty-one males, body water ranged from 40 to 68 per cent and averaged 53 per cent. In thirty-one females, and this was the first time estimations of body water had been made in women, body water ranged from 30 to 53 per cent, and averaged 45 per cent.[15] These figures were considerably lower and more variable than has commonly been accepted. Osserman et al,[13] using the same technique, namely, dilution of antipyrine, obtained a higher average figure than ours. Their average figure was 63 per cent in a group of muscular young men and muscle has a high water content. Using deuterium oxide, Francis Moore and his group in Boston[16] have now carried out elegant studies on the total water content in a group of seventeen young males and eleven young females. The males average 62 per cent water and the females, 52 per cent. These figures, too, are higher than ours and, for males, agree closely with Osserman's figures. It may be that our figures are lower because of the nature of the subjects. Many of them were older and lived in a chronic disease hospital. They may therefore be less well muscled and perhaps fatter.

These low figures for total body water warranted re-examination of the question as to the distribution of water inside and outside cells. Several methods for measuring extracellular fluid have been in use. Bromide and thiocyanate have perhaps been used most widely. More recently, radio sodium and chloride have been used. In these studies, bromide was used as a measure of what has been termed the chloride or extracellular fluid space.

The volume of dilution of sodium bromide was measured simultaneously with the dilution of antipyrine in these eighty-two subjects and intracellular water was then calculated as the difference between the total (antipyrine) and extracellular (chloride) water.[17] Calculated in this way, the intracellular water averaged 15.3 L. in males and in females 11.1 L. Such values for intracellular water seemed much too small to be credible. For example, the average male of this series weighed 62.6 K. According to Morales and associates[18] 40 per cent of body weight is muscle. This average male has, then, 25 K. muscle which contains about 78 per cent water. Muscle alone would then require 19.5 L. of water of which the maximum of 10 per cent may be esti-

mated as extracellular on the basis of chloride. This leaves a minimum of 17.5 L. of intracellular water for muscle alone when the entire intracellular water was estimated as 15.3 L. on the basis of bromide as a measure of extracellular water.

In the light of more precise knowledge of total body water it became clear that the existing methods for measuring extracellular fluid over-estimated the size of that body of water. This fact was not unexpected. It has become increasingly apparent that sodium and chloride enter many cells of the body. For instance, chloride ions are known to enter the cells of gastric and intestinal mucosa, of sweat and salivary glands, of renal tubules, of liver and the red blood cells.

A more accurate measure of extracellular fluid was plainly needed. Inulin was chosen as a trial substance because it is known not to enter the red cells and the kidney cells and its molecular size makes it unlikely that it enters other cells of the body. The difficulties of using inulin to measure extracellular space are, however, great. It is excreted rapidly and diffuses slowly. There are inherent errors which tend toward making the inulin space as measured larger but never smaller than the actual value obtained. Some of these difficulties have been alleviated by the work of Schwartz, Gaudino and Levitt[19, 20] in Dr. Homer Smith's laboratory, aided by Dr. Gomez' mathematical genius.

Measurements of extracellular space by dilution of inulin have also been made in this laboratory.[17] In order to obtain equilibrium an infusion of inulin at a constant rate was maintained for ten to fourteen hours. The infusion was stopped and the inulin excreted in the urine in the subsequent forty-eight hours taken as the amount in the body at the end of the infusion. Inulin space was calculated by dividing this amount by the concentration of inulin in the plasma water at the time the infusion was stopped. In four individuals the dilution of bromide (i.e., chloride space) was measured simultaneously with inulin. The average chloride space was 17 L. and the inulin, 10 L. If the volume of dilution of inulin is accepted as a measure of extracellular fluid, then the amount of the extracellular fluid is, as seemed likely, much less than has previously been thought. Since total body water in these four subjects averaged 35 L. as measured by dilution of antipyrine, 25 L. are left for intracellular water on the basis of inulin space, a much more reasonable figure than the 17 L. obtained by subtracting the chloride space.

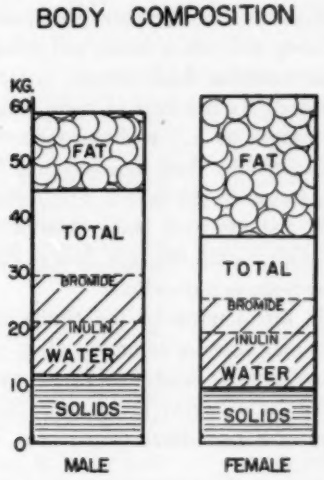

Fig. 3. Total body water and its division between the intra- and extra-cellular phase according to the method used for estimation of extracellular fluid.

To accept the figure based on dilution of inulin for the anatomical extracellular space requires rearrangement of certain fairly well established concepts. First, at face value it means that a considerable portion of chloride of the body is inside cells. Bromide is known to be distributed in tissues in proportion to their chloride content[21] in much the same manner that radio chloride would be distributed through body chloride. Thus bromide is diluted in the total chloride of the body rather than in any given body of fluid. Hence, its degree of dilution becomes a measure of the total amount of chloride rather than a measure of extracellular space. In accordance with this suggestion estimations of total chloride were made in fifty-two normal subjects (26 males, 26 females).[22] Total body chloride was calculated as follows:

$$\frac{\text{Total Body Chloride}}{\text{Residual Bromide in Body}} = \frac{\text{Concentration of Chloride in Plasma}}{\text{Concentration of Bromide in Plasma}}$$

The mean total body chloride of the males (average weight 65.2 K.) was 2039 mEq, that of the females (average weight 67.6 K.) was 1897

mEq. Using the volume of distribution of inulin as the best measure of extracellular fluid volume, an estimate was then made as to what portion of the total body chloride is inside and what portion is outside cells. The average extracellular fluid volume, as measured by dilution of inulin, is approximately 15 per cent of body weight[17, 19, 23, 24] or for this group (average weight 66 K.) 10 liters and contains 110 mEq of chloride per liter. Extracellular fluid thus accounts for only 1100 mEq of the total chloride found in the body. The difference between the extracellular chloride and the total body chloride is about 900 mEq which represents chloride within the cells. It is evident that almost half of the chloride in the body is intracellular.

Reconstruction in broad terms of the composition of an average man of 60 K. weight may serve as summary (Fig. 3). Twelve kilos or one-fifth is solid, extracellular water 10 L. or roughly 15 per cent body weight, intracellular water 25 L. or about 40 per cent of body weight, and the rest, 13 K., or about 25 per cent, is fat.

Conclusions

1. Measurement of body water by several procedures suggests that body water comprises a smaller and more variable proportion of body weight than has previously been thought.

2. The variability of water content is due chiefly to the great variability of the fat stores of the body.

3. When intracellular water is calculated as the difference between total water and extracellular water as estimated by the dilution of bromide, the volume of intracellular water appeared to be too small because the measures of extracellular fluid generally employed (bromide, thiocyanate) appear to over-estimate the size of the extracellular space.

4. If the dilution of inulin is accepted as a more accurate measure of extracellular water, then nearly half the chloride ions are inside cells.

5. It would appear that about one-fourth of the total water of the body is extracellular and three-fourths intracellular.

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CORRECTION

Drs. Maurice Bruger and Elliott Oppenheim wish to take this opportunity to correct a misquotation from Dr. Eli Moschcowitz' monograph on "Vascular Sclerosis" (Oxford University Press, New York, 1942) which they inadvertently made in their paper entitled 'Experimental and Human Atherosclerosis: Possible Relationship and Present Status" which was published in the Bulletin of The New York Academy of Medicine, September 1951.

The quotation "Moschcowitz has stated that without increased intravascular pressure there can be no arteriosclerosis" should read "Moschcowitz has emphasized the role played by intravascular pressure in the genesis of arteriosclerosis." It should be pointed out that Dr. Moschcowitz stated in his monograph that prolonged normal intravascular tension might also produce arteriosclerosis provided the individual lived long enough.

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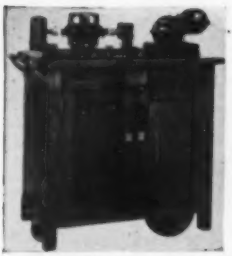

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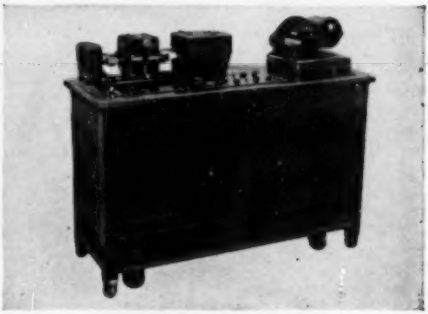

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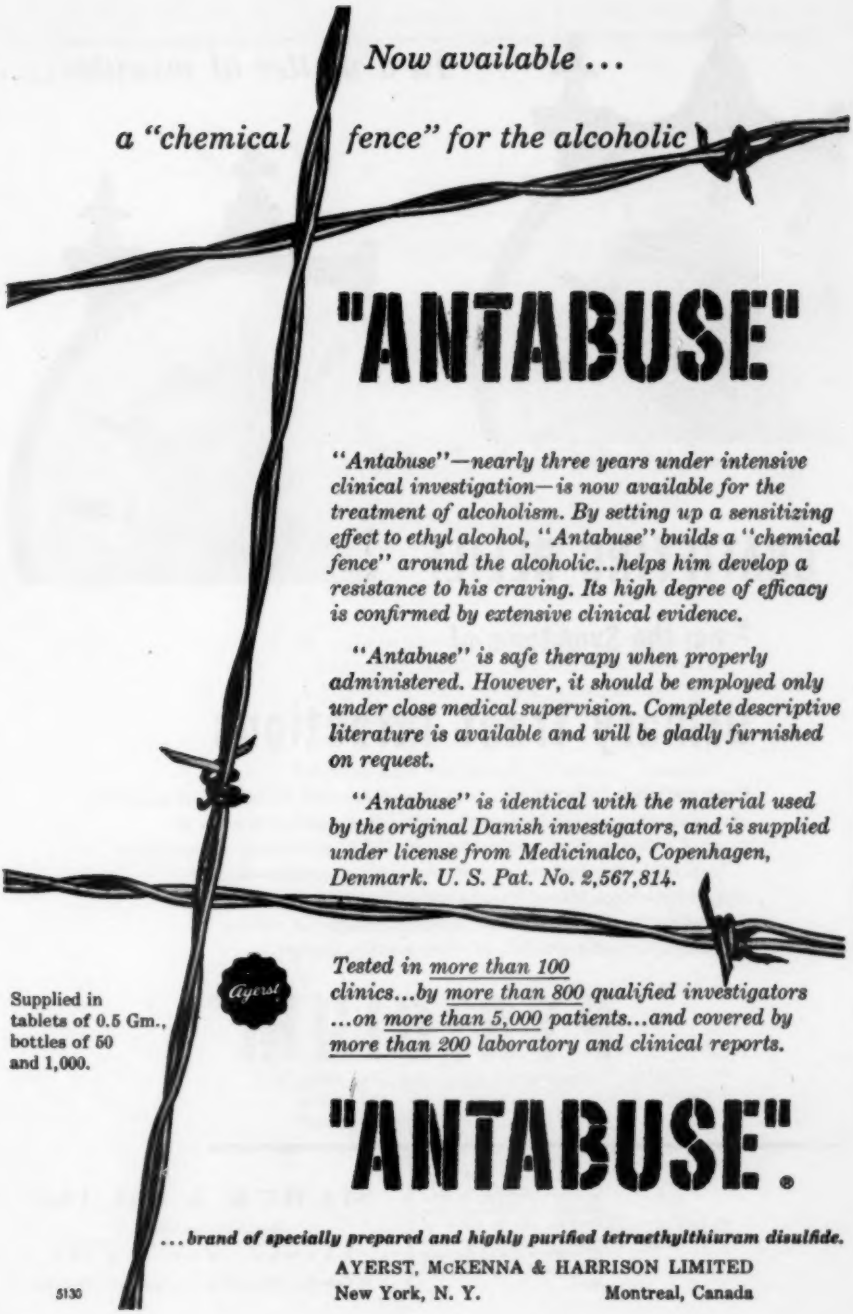

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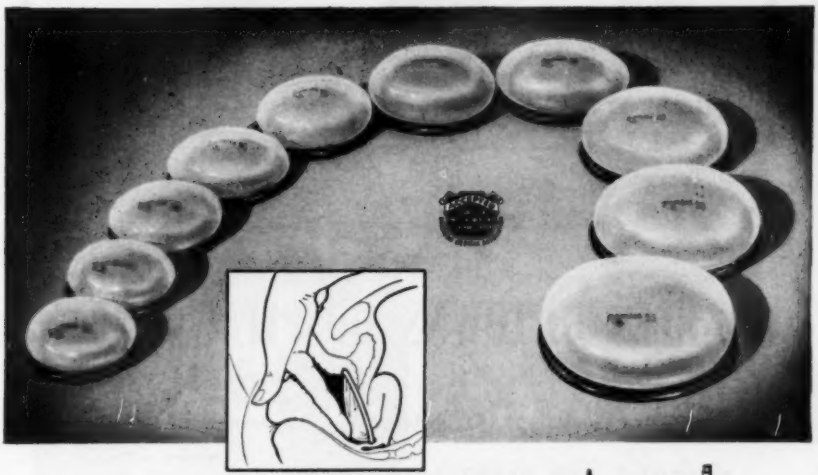

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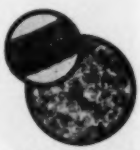
1. Clark, Le M.: The Vaginal Diaphragm. St. Louis, C. V. Mosby Company, 1938, p. 43.
2. Dickinson, R. L.: Techniques of Conception Control. Baltimore, Williams & Wilkin Company, 1950, p. 17.

Unretouched photomicrograph of the dome (enlarged 10 diameters) and the rim (inset) of a "RAMSES" Flexible Cushioned Diaphragm.



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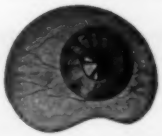

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*Gosselin, George A., M.D. *Neurology and Physiology in Functional States* *Connecticut State Medical Journal 15: 109-113, (February) 1951*

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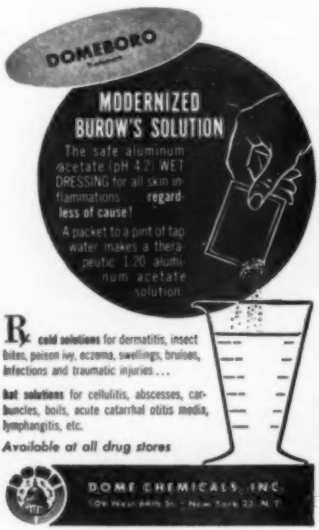
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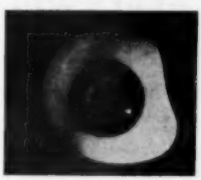

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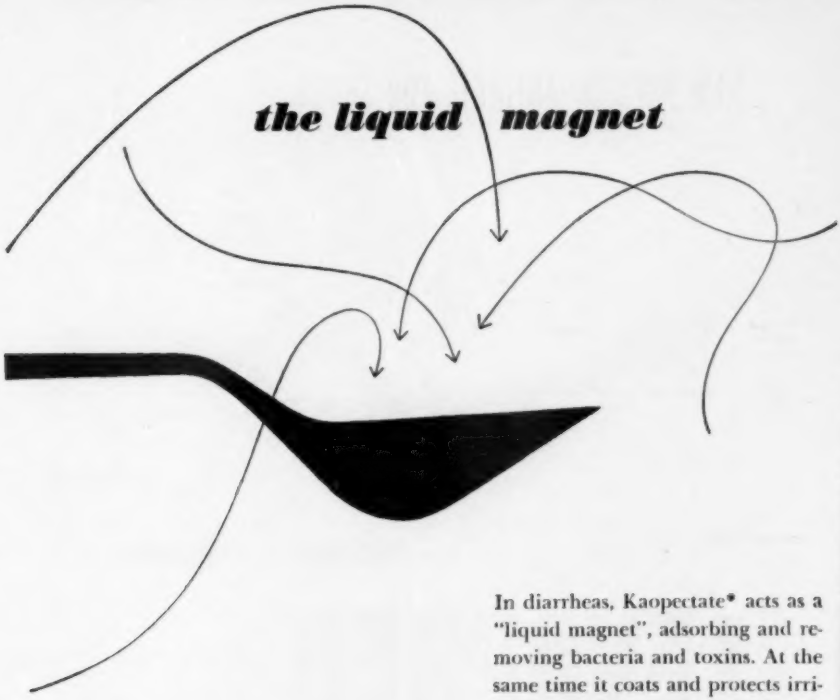

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1. Phillips, O.C., and Nicholson, M. J.: Surg. Clin. North Am., 30:705, June, 1950.
2. Wilson, C.M., and Bassett, R.C.: Univ. Michigan Med. Bull., 16:57, March, 1950.

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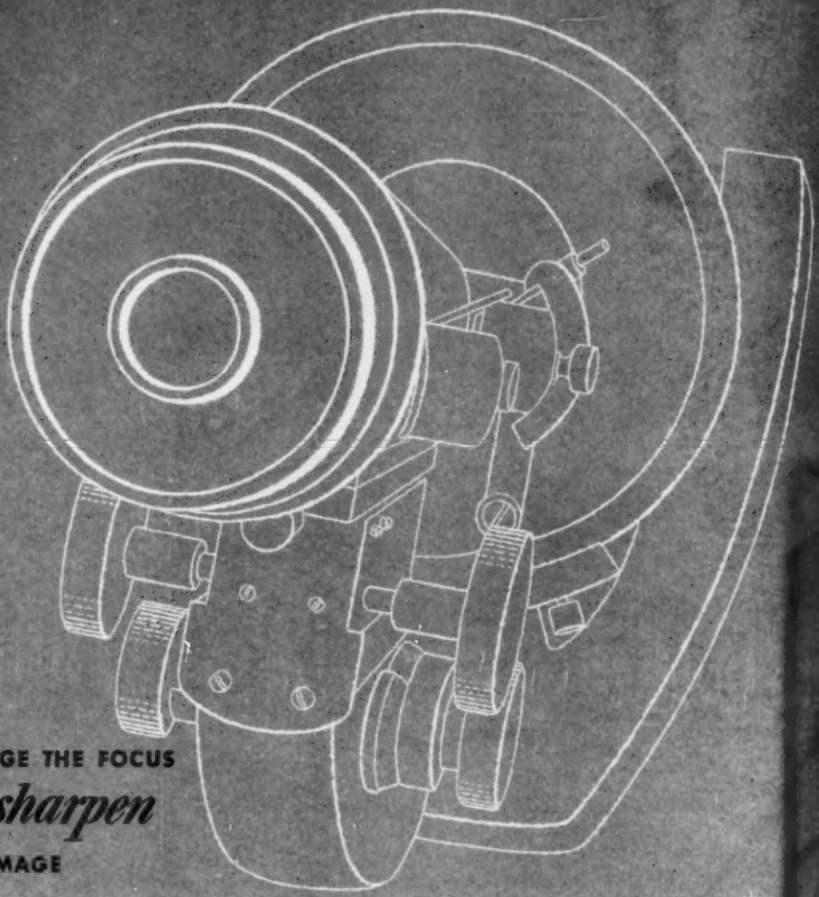

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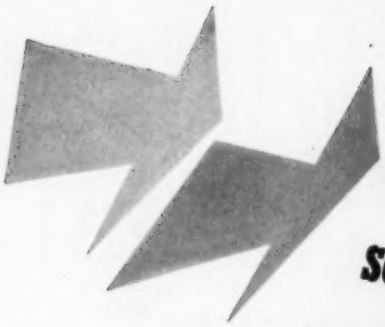

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Editorial: J.A.M.A. *135*:576, Nov. 1, 1947.

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Griggs, D. E., and Johns, V. J.: California Med. *69*:133, Aug. 1948.

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Blake, R. C., Arnold, M., Lund, Pearce, R. D.: J.A.M.A. 144: 1161 (July 29), 1950.

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